Exhibit 2

Virginia Commonwealth University

Medical College of Virginia

February 2, 1982

Hadrian R. Katz, Esquire
Arnold & Porter
1200 New Hampshire Avenue, N.W.
Washington, D. C. 20036

Dear Mr. Katz:

As you requested, I have reviewed the October 22, 1981, letter from Dr. Gio Batta Gori of the Franklin Institute Policy Analysis Center, and the monograph by Drs. T. D. Darby and James E. McNamee of the University of South Carolina School of Medicine entitled, "Use of Cotinine Blood Concentration As A Detection Method of Nicotine Delivery With Cigarette Smoking." The study conducted by Dr. Gori and additionally interpreted by Drs. Darby and McNamee purports to draw conclusions about the nicotine delivery of cigarettes based on measurements of the cotinine level in a smoker's plasma at periods of time after switching to the cigarette brand in question. These papers present some rather novel and creative reasoning, but too often rest upon assumptions that do not appear to be supported by either the experimental data obtained in the study, or by previous scholarship. Some of the unresolved problems and questions, as I see them, follow:

Available data support the view that increases in nicotine dose will result in increases in production of its metabolite cotinine with resultant increases in plasma concentration of cotinine. But, the relationship between the two increases is not likely to be simple and further data are needed before confident interpretations can be made. Some reasons for this follow:

1. It has been shown that increase in nicotine dosage results in an increase in the urinary excretion of unchanged nicotine (1,2) as well as in the per cent of the dose excreted (1). Per cent increase is linear with dose in the dog (1) but predictive information is needed for man.

2. The level of urinary excretion of cotinine has been judged by some investigators to be a measure of degree of nicotine exposure (3,4). Interrelationship data between excreted cotinine and plasma levels are needed since plasma cotinine unlike excreted cotinine remains susceptible to biotransformation.

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3. Cotinine undergoes biotransformation and the rate of this may increase with increasing concentration of cotinine in the body, but data as to degree are lacking, thus further complicating the use of plasma cotinine as a measure of nicotine dosage.

Studies have also been interpreted to show that smokers tend to self-titrate their nicotine dosage when switching from high-to-low and vice-versa nicotine delivery cigarettes (6,7). This factor is recognized by Dr. Gori, but the evidence for it is dismissed as "fragmentary," ... "and the precise relationship can not be predetermined at the present state of the art," and a prediction is offered that "a direct comparison of smokers of high and low yield cigarettes would probably require a large number of subjects in order to reach statistical significance, and it is likely to be difficult to interpret unless differences between cigarettes were very high." (See Page 4 of Dr. Gori's report.)

None-the-less, to hopefully circumvent the above problem, Study B was designed to include only subjects who customarily smoked cigarettes of 0.1 mg (sic) nominal nicotine delivery for the comparative change in plasma cotinine levels on switching to the Barclay 0.2 mg (sic) nominal nicotine delivery cigarettes. Let it be noted that this is still a two-fold difference and in the study referenced (6) above the problem became evident between cigarettes with a maximum three-fold difference in nominal nicotine delivery.

Concerning the report by Drs. Darby and McNamee, their analysis includes the assumption that a flat 70% of absorbed nicotine is eventually converted to cotinine. I have found no supporting data for this assumption and, indeed, it is unsupportable, since it has been shown that with increasing dose of nicotine an increasing per cent of the dose is excreted unchanged in the urine (1).

A search for data supporting a half-life of 30 hours for plasma cotinine in man has also been unrewarding. A number of articles containing this statement have been found, but where referenced it has been to other articles including the same statement without revealing supporting data. All lower animal data indicate shorter half-lives for cotinine. Data for man is needed. Also needed is recognition that cotinine also undergoes biotransformation (5) and "... average renal function and normal urinary output ..." are not the sole criteria for elimination of cotinine from the body.

In summary, the Gori and Darby and McNamee papers evidence unsupported assumptions as well as omissions of consideration of available knowledge critical to interpretation of findings. I do not consider it possible to draw any conclusions from these papers about the relative characteristics of the specific brands of cigarettes studied.

Sincerely yours,

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